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Solid-phase synthesis of unnatural α-amino acid derivatives using a resin-bound glycine cation equivalent

Martin J. O'Donnell,[a,*] Francisca Delgado,[a] Mark D. Drew,[a,†] Richard S. Pottorf,[a,‡] Changyou Zhou[a,§] and William L. Scott[b]

[a]*Department of Chemistry, Indiana University-Purdue University at Indianapolis, Indianapolis, IN 46202, USA*
[b]*Research Technologies and Proteins, Lilly Research Laboratories, Indianapolis, IN 46285, USA*

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Abstract

Unnatural amino acids were synthesized on solid-phase by reaction of a resin-bound Schiff base with organoboranes. This novel use of a resin-bound glycine cation equivalent allows for the preparation of a variety of amino acid structural types not readily available by the complementary anionic equivalent.

Keywords: amino acids; amino acid derivatives; boron; boron compounds; solid-phase synthesis.

Schiff base esters have been used as both anionic and cationic synthons for the preparation of a variety of amino acid derivatives. Phase-transfer catalysis (PTC) involves the reaction of anionic glycine and higher amino acid equivalents with electrophiles.[1] The complementary cationic systems make use of the reaction of several nucleophilic species with cationic glycinates.[2,3] Catalytic enantioselective variants of both systems have been developed in our laboratory[4,5] and by others.[6,7] Recently we have extended this chemistry to the resin-bound synthesis of unnatural amino acids and peptides, termed 'UPS' (unnatural peptide synthesis) by the reaction of resin-bound glycine (**1**) or higher amino acid anion equivalents with electrophiles[8] (Scheme 1). We now report the preparation and use of a resin-bound glycine cation equiv-

1 (Ref. 8) 2

Scheme 1. Resin-bound glycine anion (**1**) and cation (**2**) equivalents

* Corresponding author. E-mail: odonnell@chem.iupui.edu
† Present address: Rhône-Poulenc Rorer, 500 Arcola Road, Collegeville, PA 19426, USA.
‡ Present address: Provid Research, 10 Knightsbridge Road, Piscataway, NJ 08854, USA.
§ Present address: Merck Research Laboratories, Rahway, NJ 07085, USA.

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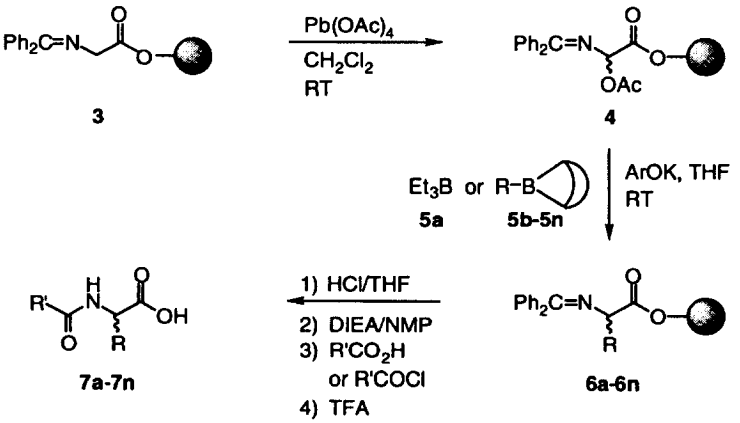
alent (**2**), which can be reacted with organoboranes. Since organoboranes can be prepared from alkenes or organolithium reagents, this methodology provides access to several amino acid structural classes that are difficult to prepare by normal alkylative procedures.

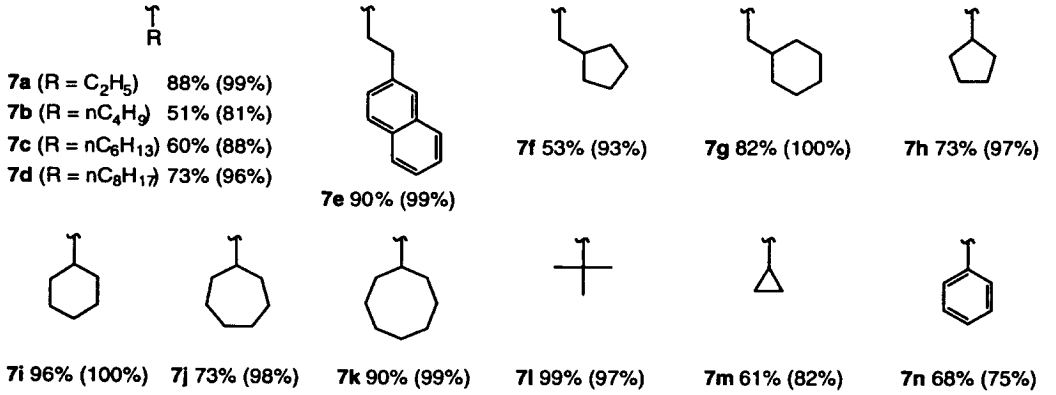
The reaction of organoboranes with anions containing a leaving group, first reported by Brown and co-workers in 1968,[9] has been used in a number of syntheses.[10] The preparation of amino acid derivatives from organoboranes was accomplished by reaction of a Schiff base acetate derivative [$Ph_2C{=}NCH(OAc)CO_2Et$] with 9-alkyl- or 9-aryl-9-BBN in the presence of a hindered phenoxide base.[3a] The method was extended to the synthesis of α-aminophosphonic acid derivatives by reaction of organoboranes with an α-aminophosphonate cation equivalent.[3b]

The reaction of organoboranes with a solid-phase glycine cation equivalent requires the preparation of the resin-bound acetate (**4**), which was accomplished by treatment of the Schiff base of Wang resin bound glycine (**3**)[11] with lead tetraacetate in CH_2Cl_2 at room temperature (Scheme 2).[12]



Scheme 2. Synthesis and reaction of the resin-bound acetate **4** with organoboranes

The 9-alkyl- or 9-aryl-9-BBN derivatives used in this study were prepared by two established routes: hydroboration of an alkene with 9-BBN[12a] or reaction of an organolithium with 9-methoxy-9-BBN.[12b] Various types of olefins (monosubstituted alkenes for **5c–5e**, methylenecycloalkanes for **5f** and **5g**, and cycloalkenes for **5h–5k**) were reacted with 9-BBN to give organoboranes **5c–5k**, which were then used as described below in the reaction with acetate **4**. Organoboranes **5b** and **5l–5n** were prepared by reaction of the organolithium reagent with 9-methoxy-9-BBN and were generally purified by vacuum distillation prior to reaction with acetate **4**.



Scheme 3. R-groups in **5–7** and yields of *N*-quinaldoyl derivatives **7** [yield (purity)]

Reaction of **4** with either triethylborane (**5a**) or a 9-alkyl- or 9-aryl-9-BBN (**5b–5n**) with resin-bound acetate **4** in THF in the presence of potassium 2,6-di-*tert*-butyl-4-methylphenoxide, gave the resin-bound product **6**. Derivatization and release of the products from the resin was accomplished using our normal methodology of imine hydrolysis, neutralization, *N*-acylation and final cleavage from the resin with TFA to give products **7**. *N*-Acylation was typically accomplished with quinaldic acid to provide the UV-active *N*-quinaldoylated derivatives (Scheme 3).[14] The Fmoc- and Cbz-derivatives were also prepared from **6a** [87% (94%, HPLC) for **7a** (R′CO=Fmoc) and 59% (98%, NMR) for **7a** (R′CO=Cbz)].[15]

In summary, organoboranes have been reacted with acetate **4**, which serves as a resin-bound α-cationic glycine equivalent, as a route to a variety of amino acid derivatives.

1. Typical experimental procedures

Preparation of resin-bound acetate (4): The benzophenone imine of Gly-Wang resin[11] (**3**, 1.79 g, 0.47 mmol/g, 0.84 mmols) was placed in a 25 mL reaction vessel (RV, see Scott et al.[13] for a description of the reaction apparatus) and washed with CH_2Cl_2 (3×20–25 mL) using argon to purge the vessel (unless otherwise noted, this same protocol was used for each 'wash' in this sequence). CH_2Cl_2 (10 mL) was added followed by $Pb(OAc)_4$ (95%, 589 mg, 1.26 mmols) in CH_2Cl_2 (5 mL) and then additional CH_2Cl_2 (5 mL) was added. The reaction mixture was rotated overnight (the resin turned an immediate purple color and then a yellow color with a white ppt after 1–2 h). The resin was filtered and washed thoroughly with CH_2Cl_2 (six times), THF, THF:H_2O (3:1) (four times), THF, and finally CH_2Cl_2. The resin product (**4**) was dried in vacuo at ambient temperature and is stable for several weeks if stored under argon in the freezer. Gel-phase ^{13}C NMR indicated that this reaction proceeds in excellent yield [loss of methylene signal in **3** (55.59 ppm); appearance of methine (84.08 ppm) and methyl (20.86 ppm) signals in **4**]. A control using Et_3B, as described below, is routinely run to monitor the quality of **4**.

Preparation of organoboranes (5) from alkenes: A 15 mL two-necked round-bottom flask, equipped with a septum inlet, a condenser, a magnetic stirring bar and a gas inlet tube for argon blanketing, was connected to a vacuum line, flamed under reduced pressure and cooled with argon flushing. The dried flask was charged with 9-BBN (0.5 M in THF, 2.0 mL, 1.0 mmol) and the alkene (1.05 mmol, 1.05 equiv.) was added. The reaction mixture was stirred at room temperature for 15 min, refluxed for 1 hour and then cooled to room temperature. This 9-R-9-BBN stock solution, prepared immediately prior to use, was used directly as a 0.50 M THF solution.

Preparation of organoboranes (5) from organolithiums: A 100 mL round-bottom flask, equipped and dried as above, was charged with *B*-methoxy-9-BBN (1.0 M in hexanes, 20 mmol), the solution was cooled to −78°C, and the organolithium reagent (1.0 M solution in cyclohexane or pentane, 20 mmol) was added. The reaction mixture was stirred for 30 min at −78°C, warmed to room temperature and stirred overnight. The reaction mixture was filtered, the solid was washed with pentane (10 mL), the filtrate and washes were combined, the solvent was removed and the organoborane **5** was distilled under vacuum. Immediately prior to use in the following reaction, a 0.50 M THF solution of the organoborane **5** was prepared.

*Preparation of 2,4-di-*tert*-butyl-4-methylphenoxide solution*: A 10 mL round-bottom flask, equipped and dried as above, was charged with 2,6-di-*tert*-butyl-4-methylphenol (0.22 g, 1.0 mmol) in dry THF (2.0 mL), and then immersed in an ice bath. KO^{t}Bu (1.0 M solution in THF, 0.95 mL, 0.95 equiv.) was added dropwise over 5 min by syringe and the reaction mixture was stirred at 0°C for 30 min. The phenoxide base stock solution (0.34 M in THF) was prepared just prior to use.

Reaction of resin-bound acetate with organoboranes: Compound **4** (50 μmol, 109 mg, substitution=0.46 mmol/g) was placed in a 3.5 mL RV, washed with CH_2Cl_2 (3×1.5–2 mL using argon to

purge the vessel; unless otherwise noted, this same protocol was used for each 'wash' in this sequence). The resin was washed with dry THF (three times). THF (1 mL) was added followed by the Et_3B/THF or 9-R-9-BBN/THF solution (**5**, 2 equiv., see above) and the potassium 2,4-di-*tert*-butyl-4-methyl-phenoxide/THF solution (1.3 equiv., see above). The reaction mixture was rotated overnight, then washed with THF followed by THF/H_2O to give resin-bound product **6**.

Imine hydrolysis: 1N HCl:THF (1:2, 1.5–2 mL) was added to the resin-bound product **6** (50 μmol) in the RV. The mixture was rotated for 4 h, filtered, and washed with THF (3×1.5–2 mL), neutralized with 10% DIEA/NMP (3×1.5–2 mL), and washed with NMP, CH_2Cl_2, and NMP (3×1.5–2 mL each).

N-*Acylation*: NMP (1.20 mL) was added to the resin-bound amino acid in the RV followed by the acylating reagents [Cbz: 1 M NMP solution of benzyl chloroformate (250 μL, 5 equiv.), and DIEA (44 μL, 5 equiv.); Fmoc: 1 M NMP solution of fluorenylmethyl chloroformate (250 μL, 5 equiv.), and DIEA (44 μL, 5 equiv.); quinaldoyl: 1 M solution of quinaldic acid (250 μL, 5 equiv.), 1 M NMP solution of HOBt·H_2O (250 μL, 5 equiv.) and DIC (39 μL, 5 equiv.)]. The mixture was rotated for 18 h, filtered, and washed with NMP, THF and CH_2Cl_2 (3×1.5–2 mL each).

Cleavage from the resin: 95% TFA/H_2O (1.5–2 mL) was added to the resin-bound *N*-acylated amino acid (50 μmol) in the RV. The mixture was rotated for 4 h and then filtered into a tared vial. The resin was washed with TFA/H_2O and then CH_2Cl_2 (3×1.5–2 mL each). The solvent from the combined filtrate and washes was removed under reduced pressure and the residue was dried in vacuo to give product **7**. Mass recovery yield was determined by weight (range=10.2–22.4 mg). The purity of products **7** was measured by HPLC analysis. A ZORBAX SB-C18 column (4.6×75 mm) with mobile phases of 0.1% (v/v) TFA/H_2O (A) and 0.08% (v/v) TFA/CH_3CN (B) at a flow rate of 1.0 mL/min and UV detection at 250 nm. A gradient of 20–100% B over 25 min was used for compounds **7a** (R′=quinaldoyl, R′CO=Fmoc and Cbz), **7b–7c**, **7f–7i**, and **7l–7n**. A gradient of 40–100% B over 25 min was used for compounds **7d**, **7e**, **7j** and **7k**. All products **7** gave high resolution mass spectra and NMR spectra (see the literature[14,15]) consistent with the assigned structures.

Acknowledgements

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14. Representative ^{1}H NMR spectra for compounds **7** (R′=quinaldoyl) (300 MHz, CD_3CN): **7a**: 1.02 (t, 3H, J=7.4 Hz); 1.84–2.11 (m, 2H); 4.61 (td, 1H, J=7.4 and 5.2 Hz); 7.70 (app. t, 1H, J=7.4 Hz); 7.85 (app. t, 1H, J=7.4 Hz); 8.02 (d, 1H, J=8.1 Hz); 8.16 (d, 1H, J=8.8 Hz); 8.20 (d, 1H, J=8.8 Hz); 8.47 (d, 1H, J=8.8 Hz); 8.65 (d, 1H, J=5.2 Hz). **7g**: 0.90–2.05 (m, 13H); 4.72 (app. q, 1H, J=7.7 Hz); 7.71 (app. t, 1H, J=7.4 Hz); 7.87 (td, 1H, J=8.1 and 1.5 Hz); 8.02 (d, 1H, J=8.1 Hz); 8.19 (app. t, 2H, J=8.1 Hz); 8.48 (d, 1H, J=8.1 Hz); 8.60 (d, 1H, J=8.1 Hz). **7i**: 1.10–1.34 (m, 4H); 1.64–1.79 (m, 6H); 1.90–2.05 (m, 1H); 4.58 (dd, 1H, J=8.5 and 5.5 Hz); 7.72 (app. t, 1H, J=7.4 Hz); 7.87 (app. t, 1H, J=7.4 Hz); 8.03 (d, 1H, J=8.1 Hz); 8.20 (app. t, 2H, J=8.1 Hz); 8.51 (d, 1H, J=8.1 Hz); 8.63 (d, 1H, J=8.1 Hz). **7l**: 1.11 (s, 9H); 4.50 (d, 1H, J=8.8 Hz); 7.70 (app. t, 1H, J=7.4 Hz); 7.85 (dd, 1H, J=7.4 and 8.5 Hz); 8.02 (d, 1H, J=8.1 Hz); 8.19 (app. t, 2H, J=8.5 Hz); 8.48 (d, 1H, J=8.8 Hz); 8.70 (d, 1H, J=8.1 Hz). **7m**: 0.45–0.72 (m, 4H); 1.26–1.42 (m, 1H); 3.99 (app. t, 1H, J=8.5 Hz); 7.71 (td, 1H, J=8.1 and 1.5 Hz); 7.86 (td, 1H, J=7.7 and 1.5 Hz); 8.02 (d, 1H, J=8.1 Hz); 8.18 (d, 1H, J=8.1 Hz); 8.19 (d, 1H, J=8.1 Hz); 8.47 (d, 1H, J=8.1 Hz); 8.71 (d, 1H, J=5.1 Hz).
15. NMR Spectra (300 MHz, CD_3CN): **7a** (R′CO=Fmoc): 0.94 (t, 3H, J=7.4 Hz); 1.68 (sext, 1H, J=7.4 Hz); 1.81 (sext, 1H, J=7.4 Hz); 4.06 (td, 1H, J=7.4 and 5.2 Hz); 4.25 (dd, 1H, J=13.6 and 7.4 Hz); 4.33 (d, 2H, J=7.4 Hz); 5.98 (d, 1H, J=5.2 Hz); 7.33–7.45 (m, 4H); 7.59–7.71 (m, 2H); 7.84 (d, 2H, J=7.4 Hz). **7a** (R′CO=Cbz): 0.93 (t, 3H, J=7.4 Hz); 1.68 (sext, 1H, J=7.4 Hz); 1.82 (sext, 1H, J=7.4 Hz); 4.07 (td, 1H, J=8.1 and 5.2 Hz); 5.07 (s, 2H); 5.92 (d, 1H, J=5.2 Hz); 7.24–7.40 (m, 5H).